I. PATHOLOGY OF ANEMIA II

HEMOLYTIC ANEMIA DUE TO INTRINSIC (INTRACORPUSCULAR) ABNORMALITIES OF RED CELLS (continued)

A. Thalassemias - a group of genetic disorders characterized by lack, or decreased synthesis, of either alpha or beta-globin chains of hemoglobin A.

1. α-thalassemia: α-globin chain synthesis is reduced.

2. β-thalassemia: β-globin chain synthesis is absent (β °-thalassemia) or deficient (β + -thalassemia).

3. Hematologic consequences of diminished synthesis of one globin chain derive from:
   a. Low intracellular hemoglobin (hypochromia).
   b. Relative excess of other chain.

4. α-thalassemia
   a. Adult hemoglobin (HbA) contains two α-chains and two β-chains. The α-chains are coded by one pair of α-genes on each chromosome 16. Most α-thalassemias are due to deletion(s) of α-globin gene locus (or loci); therefore, four possible degrees of α-thalassemia may result.
   b. Clinical manifestations: Non-alpha chains generally form more soluble and less toxic aggregates than those derived from alpha chains.

5. β-thalassemia
   a. The beta-chains are coded by β-globin genes on each chromosome 11. Common forms of β-thalassemia are due to point mutations or small insertions or deletions within the β-globin gene that results in errors of transcription, RNA processing, or translation.
b. Anemia in β-thalassemia is due to 1) reduced synthesis of β-globin leading to inadequate HbA formation and 2) the hemolytic component of the disease due to the relative excess of α-globin chains (forming insoluble aggregates which damage cell membranes, reduce membrane plasticity, and render red cells susceptible to phagocytosis by mononuclear phagocyte system).

c. Clinical manifestations: Symptoms begin to appear as production of HbF normally diminishes and is replaced by HbA. In thalassemia major, the marrow space is expanded, causing skeletal deformities; hepatosplenomegaly from extramedullary hematopoiesis causes abdominal distension. Multiple transfusions are necessary, leading to excessive deposition of iron; death may result from cardiac failure from iron damage. A peripheral blood smear shows microcytic anemia and presence of target cells. Thalassemia minor usually is associated with a minor microcytic hypochromic anemia. (Must be distinguished from iron deficiency.) Hemoglobin electrophoresis and iron studies are used to make diagnosis: HbA (α₂β²) is reduced and HbA2 (α₂δ²) is increased.

B Paroxysmal nocturnal hemoglobinuria - an unusual acquired membrane defect

1. Results from a somatic mutation affecting a pluripotent stem cell. The mutation is in the phosphatidylinositol glycan A (PIGA) gene, which is essential for the synthesis of the GPI protein anchor of the cell membrane. Deficiency of the GPI anchor leads to lack of expression of GPI-linked proteins including CD55, CD59 and C8 binding protein. These proteins are involved in inactivating the complement pathway. The affected cells (red cells, white cells, platelets) are therefore abnormally sensitive to the lytic activity of complement.

2. Intravascular hemolysis is continually or episodically prominent; the patients are predisposed to infections and venous thromboses. Other stem cell disorders such as acute leukemia and aplastic anemia may result.
II. HEMOLYTIC ANEMIA DUE TO EXTRINSIC (EXTRACORPUSCULAR) ABNORMALITIES OF RED CELLS

A. Mechanical trauma to red cells

1. The clinically important anemias in this category are those associated with cardiac valve prostheses and with narrowing or obstruction of the vasculature.
   a. Red cells are disrupted or damaged by the shear stresses from the turbulent blood flow and abnormal pressure gradients caused by mechanical heart valves (more so than with porcine valves).
   b. Red cells are damaged as they squeeze through abnormally narrowed vessels, often caused by widespread fibrin deposition in small vessels. This process is known as microangiopathic hemolytic anemia (MHA). MHA is seen in diseases such as disseminated intravascular coagulation, lupus, thrombotic thrombocytopenic purpura (TTP), and hemolytic-uremic syndrome (HUS).

2. Clinically, the extent of the hemolysis is often not a significant clinical problem except with TTP (and related HUS). Fragmented red cells known as schistocytes are seen on a peripheral smear. Patients often present with mental status changes and renal failure.
III. ANEMIA DUE TO IMPAIRED RED CELL PRODUCTION

A. Iron deficiency—a disturbance of proliferation and maturation of erythroblasts due to deficient heme synthesis

1. Iron deficiency is likely the most common form of nutritional deficiency world-wide. Low dietary intake - alone - is not often the cause of iron deficiency in the U.S. Some clinical conditions can result in malabsorption of iron (sprue, gastrectomy). An adequate diet under normal circumstances may not meet the increased demand for iron during pregnancy and infancy. The most important cause of iron deficiency in the Western world is chronic blood loss.

2. Stored iron is first depleted: serum ferritin declines and bone marrow iron is depleted. Circulating iron then decreases and the measured serum iron is low. The total iron-binding capacity (TIBC) increases, and transferrin saturation with iron decreases. Eventually the hemoglobin decreases and the red cells become small (microcytic) with reduced hemoglobin concentration (hypochromic).

3. Clinically, iron deficiency anemia is often asymptomatic until hemoglobin drops to a level at which patient experiences fatigue, cardiovascular compromise, etc. Laboratory criteria are noted above. In more severe anemias, other iron-containing enzymes may be depleted, causing nails to develop ridges and become spoon-shaped, tongue to become smooth, intestinal malabsorption to develop, and rarely, esophageal webs to appear.
B. **Megaloblastic anemias**- a disturbance of proliferation and maturation of erythroblasts due to defective DNA synthesis.

1. Two principal types of megaloblastic anemia - one caused by folate deficiency and one caused by vitamin B₁₂ deficiency. Both vitamins are coenzymes in DNA synthetic pathway. Enlargement of proliferating cells, particularly in erythroid precursors is seen in megaloblastic anemias; the enlarged red cell precursors are called megaloblasts and the corresponding large red cells are called macrocytes or macro-ovalocytes. Impairment of DNA synthesis, secondary to abnormal cell maturation and division, underlies enlargement; RNA and protein synthesis proceeds normally. The cellular nuclei are immature and the cytoplasm is fully mature: nuclear-cytoplasmic asynchrony.

2. **Vitamin B₁₂ deficiency**
   a. Many potential causes: inadequate diet, increased requirement, and impaired absorption. Abundant in all animal foods and is resistant to cooking and boiling, so dietary deficiency is generally limited only to strict vegetarians. May take years to deplete reserve. Impaired absorption could be due to intrinsic factor deficiency, pancreatitis, gastrectomy, ileal resection, ileal disease, or parasitic infections, such as fish tapeworm. "Pernicious anemia" applies to vitamin B₁₂ deficiency secondary to atrophic gastritis with failure of production of intrinsic factor (IF). IF is necessary for absorption of vitamin B₁₂ in the distal ileum. Deranged synthesis of IF appears to be secondary to an autoimmune phenomenon with destruction of gastric mucosa, chronic atrophic gastritis, and loss of parietal cells.
   b. Vitamin B₁₂ is required in 2 reactions:
i. Essential cofactor for enzyme 5-methyltetrahydrofolate-homocysteine methyltransferase; deficiency leads to decreased availability of tetrahydrofolic acid (THF). THF accepts/donates one carbon units, critical to DNA synthesis.

ii. Isomerization of methylmalonyl coenzyme A to succinyl coenzyme A; deficiency leads to increased methylmalonate

c. Clinical findings are mainly found in the alimentary tract, bone marrow, and central nervous system.

i. Alimentary tract: atrophic glossitis, chronic gastritis.

ii. Bone marrow and peripheral blood: moderate to severe megaloblastic anemia, leukopenia with hypersegmented granulocytes, mild to moderate thrombocytopenia.

iii. Neurologic changes related to involvement of the posterolateral spinal tracts, leading to sensory and motor abnormalities: "subacute combined degeneration" (spastic paraparesis, sensory ataxia, lower limb paresthesias).

3. Folate deficiency anemia

a. Folate is widely prevalent in raw foods, but quickly destroyed by cooking. Reserves are modest, but deficiency usually does not appear for months (except if demand is increased). Deficiency results from inadequate intake (either absolute or relative) or impaired absorption. Principal site for absorption is upper third of small intestine. Absorption may be hampered by acidic foods, legumes, some drugs.

b. Transported mainly as monoglutamate, then converted to tetrahydrofolate (THF).
c. Clinical findings
  i. Megaloblastic anemia identical to that in vitamin B12 deficiency.
  ii. No central nervous system abnormalities.
  iii. Prompt hematologic response following the administration of folic acid (sometimes also occurs even in vitamin B12 deficiency, but no reversal of neurologic abnormalities).

C. Anemia of chronic disease
   a. The most common anemia in hospitalized patients. Anemia of chronic disease is associated with chronic infections, immunological disorders and malignancies. The underlying cause is increased production of hepcidin which prevents transfer of iron from macrophages to erythroid precursors.

   b. Anemia of chronic disease may present as microcytic anemia with low serum iron, but can be distinguished from iron deficiency anemia based on the following parameters:
      i. High serum ferritin (in iron deficiency ferritin is low).
      ii. Low total iron binding capacity (TIBC is high in iron deficiency).
      iii. Increased bone marrow storage iron (bone marrow iron is absent in iron deficiency anemia).

D. Aplastic anemia - a disturbance of proliferation and differentiation of stem cells.

   1. Bone marrow suppression may take many forms; most often a failure or suppression of stem cells leads to a hypocellular marrow with anemia, thrombocytopenia, and neutropenia. This situation is called "pancytopenia." However, marrow suppression may affect a single cell line.
2. Aplastic anemia is frequently idiopathic. Other cases may result from a known toxic agent:
   a. Whole body irradiation.
   b. Myelotoxic drugs and chemicals
      Effects are often predictable, dose related, usually reversible: e.g., anti-neoplastic drugs, benzene, chloramphenicol. However, idiosyncratic reactions may occur: e.g., chloramphenicol, phenylbutazone, sulfonamides.
   c. Viral infections.

3. Aplastic anemia is likely secondary to heterogeneous group of distinct disorders. Evidence supports each of the following:
   a. Defective or deficient hematopoietic stem cells.
   b. Defect in bone marrow stroma ("hematopoietic microenvironment").
   c. Suppression of marrow stem cells by immune mechanisms.

4. Clinically, the signs and symptoms may develop insidiously and reflect the effects of anemia, granulocytopenia, and thrombocytopenia. The bone marrow typically is hypocellular with increased fat and small foci of lymphocytes and plasma cells. Must be distinguished from other syndromes causing pancytopenia. Prognosis is unpredictable.